Docket No. 2004D-0466

BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

Standard Process, INC.

And MediHerb Pty Ltd

COMMENTS ON

Draft Guidance for Industry:

Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act

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Introduction

Standard Process Inc. and MediHerb Pty. Ltd., are submitting the following comments in response to the Food and Drug Administration Draft Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal, Food, Drug and Cosmetic Act [Docket No. 2004D-0466].

MediHerb is an Australian based manufacturer and marketer of herbal products which are sold exclusively through health care professionals. In the United States, MediHerb products are sold through our distribution partner, Standard Process INC.

In Australia, herbal products are regulated by the Therapeutic Goods Administration (TGA) www.tga.gov.au/cm/cm.htm part of the Federal Government. Under this regulation herbal products are manufactured under full pharmaceutical cGMP and classified as therapeutic goods and complementary medicines.

It is noted that the draft Guidance for Industry of Nov 2004, gives no recognition or respect to traditional use or knowledge as an appropriate type of evidence to substantiate a structure/function claim.

The purpose of this submission is to strongly urge FDA to recognize reported traditional use and traditional knowledge, as well as scientific evidence, as appropriate evidence to support traditional use dietary supplement structure function claims.

There is precedent set in the United Kingdom, Australia and Canada for using evidence based on traditional use and knowledge to support dietary supplement herbal product claims. We are describing here in the system established in Australia for traditional use claims

The Australian Therapeutic Goods Administration (TGA) Guidelines for Levels and Kinds of Evidence to Support Indications and Claims is attached for reference or can be found at www.tga.gov.au/docs/html/tgaccevi.htm

The FDA Draft Guidelines

1. The FDA Draft Guidance document does not allow traditional use evidence as a type of evidence to support a structure function claim. 'Traditional use' is referred to only once in the document, in example 16 on page 10, where it is used in an example of inadequate substantiation, i.e." the claimed benefit would likely not be adequately substantiated because [it is not] based on scientific evidence". Example 14 is an example of inadequate substantiation where language is used which defines traditional use, "used effectively for centuries and relies on historical descriptions," however is interpreted by FDA as anecdotal. It is our view that documentary evidence of traditional use should not be characterized and dismissed as anecdotal.
2. The Draft Guidance document states, "*If there is an existing standard for substantiation developed by a government agency or other authoritative body,*

we may accord some deference to that standard." It is our position that the Australian government model sets an authoritative example of an existing standard for substantiation of claims and that the FDA should accord deference to that standard.

3. While the FDA Draft Guidance states that FDA intends to apply a standard of "competent and reliable scientific evidence" consistent with the standard that has been defined by the Federal Trade Commission, the FDA has ignored the fact that the FTC has shown respect for traditional knowledge and will allow claims based on it. I refer to the FTC's *Dietary Supplements: Advertising Guide for Industry* April 2001, which discusses claims based on traditional use (in relation to advertising materials).

   - "Claims based on historical or traditional use should be substantiated by confirming scientific evidence, or should be presented in such a way that consumers understand that the sole basis for the claim is a history of use"
   - "Advertising claims based solely on traditional use should be presented carefully to avoid the implication that the product has been scientifically evaluated for efficacy."
   - "The advertiser should make sure that the product ... is consistent with the product as traditionally administered. If there are significant differences ... in the form of administration, the formulation of ingredients, or the dose, a 'traditional use' claim may not be appropriate."

Defining Traditional Use

Some 80% of the world's indigenous populations in developing countries including Asia, Africa and South America, depend on traditional systems of medicine and botanical medicines, and the use of traditional medicines is becoming more widespread in developed countries as well. In the United States, many botanical products with histories of traditional use are marketed as dietary supplements

Traditional herbal dietary supplements are based on an extensive history of use, often measured over thousands of years. This history provides an accumulated repository of recorded systematic observation that underpins the traditional use of these dietary supplements as seen in Traditional Chinese Medicine, Western Herbal Medicine, Traditional Homeopathic Medicine and Ayurvedic medicine.

In many cases this traditional knowledge and use is not supported with scientific studies. However, any discussion of traditional use within a modern dietary supplement context is fraught with difficulty due to the lack of a definition for this term. This is a matter that was addressed by the regulatory authorities in Australia.

The Australian TGA under the advice of its Complimentary Medicines Evaluation Committee has adopted the following definition of traditional use:

> "Traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose"

It is our view that FDA should adopt a meaningful definition of traditional use for inclusion in the Draft Guidelines.

The Australian model

It is our view that FDA should look to the Australian Therapeutic Goods Administration (TGA) Guidelines for Levels and Kinds of Evidence to Support Indications and Claims as a model for traditional use substantiation of herbal dietary supplement structure function claims. A copy of these TGA Guidelines is attached for reference or can be found at www.tga.gov.au/docs/html/tgaccevi.htm

The Australian TGA allows two types of evidence to support and substantiate claims. These are:

- Evidence based on traditional use of a substance or product; and
- Scientific evidence

To make a claim based on evidence of traditional knowledge, manufactures must first assess the level of evidence supporting the claim.

The manufacturer must hold as least one of the following four sources of evidence for a general level claim and at least two of the following to make a medium level claim.

1. TGA- approved pharmacopeia
2. TGA approved monograph
3. Three independent written histories of use in the classical or traditional medical literature
4. Availability through any country's government public dispensaries for the indication claimed.

All claims based on evidence of traditional use must be worded to the effect that *'This traditional supplement has been traditionally used for (claim)".*

We strongly urge the FDA to adopt and include clear unambiguous guidelines for substantiating traditional use claims, which are in line with the Australian example above and those in the United Kingdom and Canada.

Conclusion

We strongly urge FDA to revise the Draft Guidance for Industry of Nov 2004, to state that traditional use and knowledge evidence is sufficient and appropriate evidence to support traditional use dietary supplement structure function claims and to also include clear unambiguous guidelines for substantiating such traditional use claims. FDA is assisted in this process by the fact that three health regulatory authorities from countries with well established and highly respected health regulatory systems have recently addressed this matter.

Respectfully submitted,

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Anne Holden, Director of Quality Control

Guidelines for

Levels and Kinds of Evidence to Support

Indications and Claims

For Non-Registerable Medicines,

including ComplementaryMedicines,

and other Listable Medicines

Therapeutic Goods Administration

October 2001

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EXECUTIVE SUMMARY

These guidelines have been developed to assist sponsors in determining the appropriate evidence to support indications and claims made in relation to Listable medicines. In particular, they relate to complementary medicines, sunscreens and other Listable medicines. This Executive Summary provides a brief overview of how to support indications and claims for these medicines. Before using an indication or making a claim, you are strongly encouraged to read the entire document to ensure you are fully informed of all requirements.

Indications and claims can be based on evidence of traditional use of a substance or product, and/or on scientific evidence. Indications/claims and evidence are categorised as being 'general', 'medium' or 'high' level.

How to make indications/claims based on evidence of traditional use

To make an indication or claim based on evidence of traditional use, sponsors must first assess the level of the evidence supporting the claim.

If you hold one of the following four sources of evidence, you hold general level evidence.

1. TGA-approved Pharmacopoeia.
2. TGA-approved Monograph.
3. Three independent written histories of use in the classical or traditional medical literature.
4. Availability through any country's government public dispensaries for the indication claimed.

If you hold two of the above sources of evidence, you hold medium level evidence. Of course, the evidence, whether it is medium or general level, must support the indications or claims that you intend to make for your product.

If you hold general level evidence, you can make general level indications and claims. These include indications and claims relating to:

- Health maintenance, including nutritional support;
- Vitamin or mineral supplementation; and
- Relief of symptoms (not related to a named disease, disorder or condition).

If you hold medium level evidence, you can make medium level indications and claims. These include the following kinds of indications and claims:

- Health enhancement;
- Reduction of risk of a disease/disorder/condition;
- Reduction in frequency of a discrete event;
- Aids/assists in the management of a named symptom/disease/disorder/ condition; and
- Relief of symptoms of a named disease, disorder or condition.

All indications/claims based on evidence of traditional use must be worded to the effect that *"This (tradition) medicine has been traditionally used for (indication)"*. This applies to general and medium level indications/claims.

High level indications and claims are not permitted based on evidence of traditional use.

Similar principles apply to making indications and claims based on evidence of traditional use for homoeopathic and aromatherapy products.

How to make indications/claims based on scientific evidence

To make indications/claims based on scientific evidence sponsors must first assess the level of the evidence supporting the indication/claim.

Sponsors who hold general level evidence can make general level indications and claims. General level evidence includes:

1. Descriptive studies, case series or reports of relevant expert committees;
2. Texts, such as TGA-approved Pharmacopoeias or monographs; and
3. Other evidence based reference texts.

General level indications/claims include indications/claims relating to:

- Health maintenance, including nutritional support;
- Vitamin or mineral supplementation; and
- Relief of symptoms (not related to a named disease, disorder or condition).

The following kinds of evidence constitute medium level evidence:

1. Evidence obtained from well designed controlled trials without randomisation. In the case of a homoeopathic preparation, evidence from well-designed, controlled homoeopathic proving;
2. Evidence obtained from well designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies; and
3. Evidence obtained from multiple time series with or without intervention, including within country and between country population studies.

(NOTE: In practice, the sources of most medium level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence.)

If you hold medium level evidence, you can make medium level indications and claims providing the evidence supports those indications/claims. Medium level indications/claims include indications/claims relating to:

- Health enhancement;
- Reduction of risk of a disease/disorder/condition;
- Reduction in frequency of a discrete event;
- Aids/assists in the management of a named symptom/disease/disorder/ condition; and
- Relief of symptoms of a named disease, disorder or condition.

Medium and general level indications and claims may only be made for minor, self-limiting conditions. Serious diseases or disorders may not be mentioned in medium or general level indications/claims.

High level indications/claims are indications or claims that refer to serious diseases or disorders or which relate to:

- Treatment, cure or management of any disease/disorder/condition;
- Prevention of any disease, disorder or condition;
- Treatment of a specific named vitamin or mineral deficiency diseases.

High level indications/claims require scientific evidence obtained from:

- a systematic review of all relevant randomised, controlled trials without significant variations in the directions and degrees of results; or
- at least one properly designed, randomised controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice. Advice should be sought from the TGA.

You can only make high level indications/claims for Registerable medicines. Listable medicines cannot carry high level indications and claims.

All indications/claims must be true, valid and not misleading, and should not lead to unsafe or inappropriate use of the product. Evidence must relate to the whole product or the same active constituent(s) with similar dosage regimen, dose form and route of administration to the product/ingredient for which a claim is being made. Sponsors must hold evidence in line with these guidelines before claiming an intended use or indication for a product.

Complementary Medicines Evaluation Committee's Guide to Levels and Kinds of Evidence to Support Claims

INTRODUCTION

These guidelines have been developed to assist sponsors in determining the appropriate evidence to support indications and claims made in relation to Listable medicines. In particular, they relate to complementary medicines, sunscreens and other Listable medicines. A glossary of terms used in these Guidelines is provided at Attachment 1.

The *Therapeutic Goods Act 1989* requires that at the time of Listing sponsors must hold the evidence to support indications and claims made in relation to Listable goods. All indications and claims made about therapeutic goods must be capable of substantiation – that is, evidence must be held by sponsors which demonstrates the indications and claims are true, valid and not misleading.

Listable goods are those products that meet the requirements of Schedule 4 of the Therapeutic Goods Regulations. Goods which do not meet the requirements of Schedule 4 and which are not exempt in Schedule 5, are Registrable. For guidance on the evidence requirements to support indications/claims for Registrable goods, these guidelines should be read in conjunction with other relevant guidelines published by the Therapeutic Goods Administration (TGA): for over the counter (OTC) medicines, the Australian Guidelines for the Registration of Drugs (volume 2); and for complementary medicines, the Australian Guidelines for Complementary Medicines (currently in preparation). Evidence to support indications/claims for Registrable goods must be submitted to the TGA for evaluation.

The therapeutic goods regulatory system

The regulation of complementary and other non-prescription medicines in Australia requires that they meet appropriate safety and quality standards. Registrable products are also evaluated for efficacy prior to being granted approval for their supply. These are products which contain active ingredients that are not exempt and/or which are not included in Schedule 4 of the Regulations, or that carry high level or otherwise Registrable indications/claims as defined in these guidelines[1]. The sponsors of other products, Listed medicines, must hold appropriate evidence to support indications/claims for their products at the time of Listing. This evidence may be called in and evaluated by the TGA where a safety concern arises, indications/claims appear to be misleading, or in response to a complaint.

Almost all therapeutic goods approved for marketing in Australia carry one of two identifying numbers; these are the "AUST R" or the "AUST L" number on the front of the label. However, there are certain goods that are not required to carry these labels. These are "exempt" goods, and some medical devices. Registrable medical devices are required to carry an AUST R number; but declaration of an AUST L number on Listable devices is optional.

"AUST R" products are registered products that have been evaluated for safety, quality and efficacy. "AUST L" products are Listed non-prescription medicines and medical devices. Substances in Listable medicines are recognised as being of low risk, and are those that are

[1] *Claims relating to the treatment, management, prevention or cure of diseases or disorders, or which in any other way refer to a serious disease, or treatment of specific named vitamin or mineral deficiency diseases.*

included in Schedule 4 of the Regulations. Addition of new medicinal substances to Schedule 4 requires evaluation of their safety and quality. Prior to entering the market, Listable medicinal products are assessed by sponsors against defined standards including those for levels of evidence described in these guidelines. Listable devices are also recognised as being "low risk". All therapeutic goods are subject to on-going post-market surveillance.

The evaluation of medicines and medical devices for safety, quality, and where appropriate, efficacy, is undertaken by the TGA with advice from expert committees as required. Advice is provided by the Complementary Medicines Evaluation Committee (CMEC) for complementary medicines, by the Medicines Evaluation Committee (MEC) for other non-prescription medicines, by the Australian Drug Evaluation Committee (ADEC) for prescription medicines, and by the Therapeutic Devices Evaluation Committee (TDEC) for medical devices.

Where indications/claims are made in relation to therapeutic goods, the Therapeutic Goods Administration determines the standards these indications/claims must meet – a cornerstone of these standards is the evidence which must be held to support indications/claims. Sponsors of products carry the primary responsibility to ensure that indications/claims made about products are true, valid and not misleading in line with these standards, under the Listing system for medicines. However, should a question arise about the appropriateness of evidence supporting a indication/claim, the final evaluation of that evidence will be made by the TGA. Some Registrable goods may require special approval to advertise. The Therapeutic Goods Advertising Code Council is responsible for such recommendations (TGACC).

The TGACC is responsible for ensuring that the public interest is upheld for any advertisement of a therapeutic good. There are provisions relating to the advertising of non-prescription medicines and medical devices in the *Therapeutic Goods Act 1989* (the Act), the Therapeutic Goods Regulations (the Regulations), and in the Therapeutic Goods Advertising Code (TGAC) and its supporting guidelines.

LEVELS AND KINDS OF EVIDENCE TO SUPPORT CLAIMS

The three principles relating to indications and claims about therapeutic goods are:

1. before claiming an intended use or indication, sponsors must hold adequate evidence to support all claims they make about a product;
2. claims must be true, valid, and not misleading; and
3. claims should not lead to unsafe or inappropriate use of a product.

The kinds of evidence which may support claims

There are two types of evidence which may be used to support claims[2]. These are:

- evidence based on traditional use of a substance or product; and
- scientific evidence.

How to use evidence of traditional use to support claims

Some 80% of the world's indigenous populations in developing countries depend on traditional systems of medicine and botanical medicines, and the use of traditional medicines

[2] Evidence held to support indications and claims must be in the English language, or be a Certified transcript translated from the native language.

is becoming more widespread in developed countries as well. Traditional medicines are based on an extensive history of use, often measured over thousands of years. This history provides an accumulated repository of systematic observation that underpins the use of these medicines.

Traditional use may infer community knowledge of the existence and application of a substance but does not necessarily carry with it any scientific assessment or scrutiny. For many products and substances there has been little quantifiable scientific research undertaken into their mode of action and effect. Evidence of traditional use may however be used to support claims for therapeutic goods. The following definition of 'traditional use' has been adopted by the CMEC for the purpose of these Guidelines.

Traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose.[3]

In assessing traditional use, the context of the claim is important. Most traditional forms of medicine are likely to use a mixture of substances, and certain behavioural rules promoting healthy diets and habits are likely to apply to them. In those cases, holistic principles are usually part of the therapy. Thus the theories, concepts and cultural context of the therapy need to be considered.

In forming a claim based on traditional use, products and substances which form part of traditional therapies should identify the therapy to which they belong or the paradigm in which the therapy has been traditionally used, as well as the product description/name and the symptom/indication/condition for which the product or substance is claimed to be beneficial. Traditional therapies are considered to include Traditional Chinese Medicine (TCM), traditional Ayurvedic medicine, traditional western herbal medicine, traditional homoeopathic medicine, aromatherapy and other indigenous medicines.

Modification of the classic formulations in Traditional Chinese Medicine (TCM) and Ayurvedic medicine must be based on the classical theory associated with the therapy and on traditional methods of preparation, in order for these products to make a traditional claim. For example, to meet the criteria for a traditional claim using evidence of traditional use, the overall formulation of a TCM needs to reflect the classical methods of combination. Traditional claims for combinations in Western Herbal formulations must be based on evidence linking the particular formulation (including methods of preparation) with traditional preparations, and must reflect the traditional knowledge about each individual herb in the product.

With respect to multigenerational use of homoeopathic medicines, it is recognised that homoeopathic medicine represents a special case where the manufacturing process of serial dilution is a major component of the tradition of use of the therapy. Providing that a new substance is prepared according to principles described in TGA-approved homoeopathic pharmacopoea (see Attachment 3), and satisfies safety requirements, claims may be assessed on an "evidence of traditional use" or "use in traditional practice" basis. Evidence of "traditional use" or "use in traditional practice" includes independent written histories of use in traditional or contemporary homoeopathic literature, multigenerational use, homoeopathic proving, records of clinical use and records of the set of symptoms provoked by a 'crude'

[3] Where tradition of use has been recorded as an oral rather than written history, then evidence of such should be obtained from the appropriate practitioner or indigenous group(s), who maintain such a history.

substance. Claims made in relation to homoeopathic products must be consistent with the "homoeopathic picture" of the remedy or remedies on which the claim is based.

Substances or products which have been altered significantly in their constituent profile from the classical traditional medicine on which the claim is based, require scientific evidence in order to substantiate their claimed action.

Combinations of substances, some of which have a history of traditional use, and others which do not but are supported by scientific evidence, may make indications/claims based both on their traditional-use components and the scientific evidence, thus allowing a mixed claim. Should scientific evidence be contrary to the evidence based on traditional use, the claim used must reflect the truth, on balance of the evidence available. Where a claim in its entirety is supported by scientific evidence, and the sponsor wishes to mention that the ingredient or product has a tradition of use, the particular tradition from which the ingredient was derived need not be specified. For example:

"*Echinacea* helps support the immune system especially during the winter colds and flu season. This herb has been used traditionally for hundreds of years and now scientific evidence suggests that it may assist in supporting immune function"; or

"It has been known for hundreds of years that citrus fruits contained a substance which was important for good health. We now know that substance is vitamin C, and scientific studies have shown it is essential for maintaining healthy gums, blood vessels and connective tissue. Extra vitamin C may be important for individuals under stress".

It is not always possible to access the original reference which describes the traditional use, or use in traditional practice, for a product or substance. Indications and claims based on evidence of traditional use/ practice may be supported by contemporary literature reports of the original tradition, but they must be consistent with the wording specified for claims based on evidence of traditional use.

For multi-component Listable products, traditional claims can be based on the evidence of traditional use for the product itself, or on evidence for an individual component or components about which claims are made. In any instance where a claim links the presence of an ingredient to the product indication or claim, that ingredient must contribute to that indication. Where claims of synergy are made, the evidence of traditional use must support the synergistic effect. The dose of the ingredient or ingredients mentioned in the indication or claim must be consistent with the evidence, and the composition and preparation of the product must be consistent with the principles of the tradition about which the indication or claim is made.

Where multi-component products comprise active ingredients from different traditional therapies, the therapy from which the ingredient is derived, or the paradigm in which the therapy has been traditionally used, needs to be described if the ingredient is mentioned in a claim. For example, for a product formulated from *Panax ginseng, Bacopa monnieri* and soy-derived phosphatidyl serine, a claim might be made for the product, to the effect that "This product has been formulated from traditional and modern ingredients, to help support healthy memory". This could be entered on the Australian Register of Therapeutic Goods (ARTG) as the indication for the product.

However, if the sponsor wished to highlight the ingredients, they could use any or all of the following claims:
"*Panax ginseng* has been used for thousands of years in Traditional Chinese Medicine to tonify *qi*. It helps support memory in times of fatigue and convalescence."
"*Bacopa monnieri* has a tradition of use in Ayervedic medicine for weakness of memory. It may help normal memory function."
"Soy-derived phosphatidyl serine has been shown in scientific studies help memory function in normal, healthy individuals."

How to use scientific evidence to support claims

In these guidelines scientific evidence refers to quantifiable data. Types of quantifiable scientific evidence include clinical trials in humans, epidemiological evidence, animal studies and other evidence of biological activity.

The greater the consistency of evidence across all these kinds, the greater the strength of the evidence. The strength of evidence will allow greater or lesser latitude in the nature of any claim and the wording that can truthfully be used.

The totality (balance and range), quality and relevance of the evidence to the claims are also important. The following descriptions of the meanings of totality, quality and relevance have been adapted from the United States Federal Trade Commission's (FTC's) "Business Guide for Dietary Supplement Industry Released by FTC Staff". (If readers are interested, the full version of the FTC's guidelines are available on the internet at the following website address: http://www.ftc.gov/opa/1998/9811/dietary.htm.)

Balance and range of the evidence

Studies cannot be evaluated in isolation of the surrounding context. The surrounding context of the scientific evidence is just as important as the internal validity of individual studies. Sponsors should consider all relevant research relating to the claimed benefit of their product and should not focus only on research that supports the effect, while discounting research that does not. A well-constructed literature search should normally be undertaken to help ensure that the general body of evidence on any particular topic is identified. (There are tutorials available on the internet on electronic database searching. Two such sites are:
http://www-library.uow.edu.au/InfoServ/USE/int_tut.htm; and
http://www-library.uow.edu.au/EDT/index.html.)
Balance and range of evidence may also be reflected in an authoritative review (these would normally be peer-reviewed and published).

Ideally, the studies relied on by a sponsor would be largely consistent with the surrounding body of evidence. Wide variation in outcomes of studies and inconsistent or conflicting results will raise serious questions about the adequacy of a sponsor's substantiation. Where there are inconsistencies in the evidence, it is important to examine whether there is a plausible explanation for those inconsistencies. In some instances, for example, the differences in results will be attributable to differences in dosage, the form of administration, the population tested, or other aspects of study methodology. Sponsors should assess how relevant each piece of research is to the specific claim they wish to make, and also consider the relative strengths and weaknesses of each. If a number of studies of different quality have

been conducted on a specific topic, sponsors should look first to the results of the studies with more reliable methodologies.

The Quality of the Evidence

In addition to the amount and type of evidence, quality of evidence is important. Where the claim is one that would require scientific support, the research should be conducted in a competent and reliable manner to yield meaningful results. The design, implementation, and results of each piece of research are important to assessing the adequacy of the substantiation.

There are some principles generally accepted in the scientific community to enhance the validity of test results. However, there is no single set protocol for how to conduct research. For example, a study that is carefully controlled, with blinding of subjects and researchers, is likely to yield more reliable results. A study of longer duration can provide better evidence that the claimed effect will persist and better evidence to resolve potential safety questions. Other aspects of the research results — such as evidence of a dose-response relationship (that is, the larger the dose, the greater the effect) or a recognised biological or chemical mechanism to explain the effect — are examples of factors that add weight to the findings.

Statistical significance of findings is also important. A study that fails to show a statistically significant difference between test and control group may indicate that the measured effects are merely the result of placebo effect or chance. The results should also translate into a meaningful, that is, clinically significant, benefit for consumers. Some results that are statistically significant may still be so small that they would mean only a trivial effect on consumer health.

The nature and quality of the written report of the research are also important. Research cannot be evaluated accurately on the basis of an abstract or an informal summary. However, other evidence can be considered, such as unpublished, proprietary research. The publication of a peer-reviewed study in a reputable journal indicates that the research has received some measure of scrutiny. At the same time, sponsors should not rely simply on the fact that research is published as proof of the efficacy of a substance or product. Research may yield results that are of sufficient interest to the scientific community to warrant publication, but publication does not necessarily mean that such research is conclusive evidence of a substance's or product's effect.

The Relevance of the Evidence to the Specific Claim

A common problem in substantiation of claims is that a sponsor has valid studies, but the studies do not support the claims intended to be made. Sponsors should make sure that the research on which they rely is not just internally valid, but also relevant to the specific product being promoted and to the specific benefit being claimed. Therefore, sponsors should ask questions such as: How does the dosage and formulation of the product compare to what was used in the study? Does the product contain additional ingredients that might alter the effect of the ingredient in the study? Is the product administered in the same manner as the ingredient used in the study? Has the product been tested for the same indications and claims as those proposed to be included in the ARTG? Does the study population reflect the characteristics and lifestyle of the population targeted by the product? If there are significant discrepancies between the research conditions and the real life use being promoted, sponsors need to evaluate whether it is appropriate to extrapolate from the research to the claimed effect.

In drafting indications and claims, the sponsor should take care to make sure that they match the underlying evidence support. Indications and claims that do not match the science, no matter how sound that science is, are likely to be unsubstantiated. Indications and claims should not exaggerate the extent, nature, or permanence of the effects achieved in a study, and should not suggest greater scientific certainty than actually exists. Although emerging science can sometimes be the basis for a carefully qualified claim, sponsors must make consumers aware of any significant limitations or inconsistencies in the scientific literature.

In line with these general principles for evaluating evidence, a framework for rating scientific evidence has been developed by the CMEC. This framework is adapted from the "Designation of Levels of Evidence" (National Health and Medical Research Council (NHMRC), 1999)[4] and is consistent with international best practice The rankings in the framework apply to evidence after it has been assessed with the degree of critical appraisal that would be applied by the TGA. The levels of the various kinds of scientific evidence are ranked by the CMEC as outlined in Table 1 on the next page.

All indications and claims based on scientific evidence require human studies. For those rare occasions where only non-human data exist, indications and claims may be allowed on a case-by-case basis. Supporting evidence may be used in conjunction with primary evidence to strengthen the wording of a claim.

In a claim based on scientific evidence, the recommended dosage of the product needs to be consistent with the evidence used to make the claim. The evidence must relate to the whole product or the same active constituent(s) with similar dosage regimen, dose form and route of administration to the product for which a claim is being made. When the evidence is based on an active constituent, qualification may be necessary according to how other constituents in the product may affect the activity of that constituent in the product.

A claim for a herb or herbal substance based on scientific evidence requires the herb, the part of the plant, the method of preparation and any processing, the equivalent dry weight and the dose of active or marker component to be consistent with the evidence used to make the claim. It is recognised that information about preparation and processing of ingredients could be confidential to the company providing the ingredient and therefore, not always be available to the sponsor. If this is the case, sponsors should provide evidence that the profile of the active ingredient(s) extracted using different manufacturing processes and solvents is not substantially different from the extract used in the clinical studies or other evidence used to support the claim.

[4] NHMRC 1999. *A guide to the development, implementation and evaluation of clinical practice guidelines.*

Table 1: Levels of Scientific Evidence

Level	Type of Evidence
High	Evidence obtained from a systematic review of all relevant randomised controlled trials, without significant variations in the directions or degrees of results. **OR** Evidence obtained from at least one properly designed randomised controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice. (Advice should be sought from the TGA in such cases).
Medium	Evidence obtained from well designed controlled trials without randomisation. In the case of a homoeopathic preparation [5], evidence from well-designed, controlled homoeopathic proving. **OR** Evidence obtained from well designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies. **OR** Evidence obtained from multiple time series with or without intervention, including within country and between country population studies. NOTE: In practice the sources of most medium level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements, including independently reviewed unpublished evidence, may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence.
General	Descriptive studies, case series or reports of relevant expert committees. Texts, such as TGA-approved Pharmacopoeias or monographs (see Attachment 3), or other evidence based reference texts, may be included in this Level.

Supporting evidence: Evidence derived from non-human data, such as *in vitro* studies and animal studies, and non-clinical studies such as biochemical, nutritional and microbiological studies does not stand alone and may only be used as supporting evidence.

Sponsors may wish to look at the Oxford University Centre for Evidence Based Medicine website for further qualification of types of scientific evidence. The website address is http://cebm.jr2.ox.ac.uk/docs/levels.html.

For multi-component Listable products, indications and claims can be based on the evidence for the product itself, or on evidence for an individual component or components about which indications and claims are made. In any instance where a claim links the presence of an ingredient to the product indication or claim, that ingredient must contribute to that indication or claim. Where claims of synergy are made, the evidence must support the synergistic effect. An example of how a claim for a multi-component product could be expressed as follows.

A product formulated as a "liver tonic" contains vitamins of the B-complex and *Silybum marianum*. Each vitamin is present at the Recommended Dietary Intake level, and the *Silybum marianum* is standardised to 70% silymarin. If the product had undergone clinical trial in humans and had been demonstrated to be efficacious, the claim could state to the

[5] As defined in Regulation 2, *Therapeutic Goods Regulations, 1990.*

effect that this product has been formulated as a liver tonic and clinical trials had demonstrated it to be effective in maintaining a healthy liver and it may be beneficial in improving the function of the liver. However, if the efficacy of the product as a whole had not been evaluated, the product could carry indications/claims about the potential value of each of its ingredients. For example, *B-vitamins are important for a healthy liver, and studies have shown that silymarin is of benefit in helping the liver to recover from the toxic overload of everyday life.*

The types of indications and claims which can be made based on scientific evidence are described in the section of these Guidelines commencing on page 20. Using the system of categorisation described in that section, the claims in this example are general level (health maintenance) claims, and the actual evidence to support these claims for the active ingredients is found in ME Shils, JA Olson, M Shike and AC Ross, "Modern Nutrition in Health and Disease" 9th ed, Williams and Wilkins (1999), and the Commission E Monographs. Both are evidence-based reference texts, and the information in them is largely derived from medium or even high level evidence. Hence they support the general level claims made for this product.

What kinds of indications and claims does the evidence support?

As described earlier in these guidelines there are two types of evidence which can be used to support indications and claims for therapeutic goods. These are evidence based on traditional use of a product or substance, and scientific evidence.

Indications and claims based on evidence of traditional use

In Australia indications and claims which may be made about therapeutic goods using evidence of traditional use are categorised into two levels –medium and general – according to the relative strength of the claim. Medium level indications and claims are stronger but more evidence is required to support them. This general approach is summarised in Table 2. Specific approaches have been developed for homoeopathic and aromatherapy products and these approaches are summarised in Tables 3 and 4 respectively. A summary of the definitions of the types of claims is provided at Attachment 2 to these guidelines.

Table 2: Levels and types of claims and the evidence required to support them – based on evidence of traditional use

Level of claim	Type of claim	Wording of Claim[2]	Evidence required to support claim
MEDIUM	▪ Health enhancement[1] ▪ Reduction of risk of a disease/disorder/ condition. ▪ Reduction in frequency of a discrete event. ▪ Aids/assists in the management of a named symptom/ disease/disorder/ condition.[6] ▪ Relief of symptoms of a named disease/ disorder/condition.[6]	This (tradition) medicine has been used for (indication) [3,5].	**Primary evidence**: *Two of the following four sources that demonstrate adequate support for the indications claimed:* 1. TGA-approved Pharmacopoeia.[7] 2. TGA-approved Monograph.[7] 3. Three independent written histories of use in the classical or traditional medical literature[4]. 4. Availability through any country's government public dispensaries for the indication claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:

- [1]Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- [2]Or words to this effect
- [3]Where scientific evidence is available to support the entire claim the tradition from which the medicine originated need not be specified.
- [4]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support claims.
- [5] Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations, for example "Shen" not "Kidney" in TCM.
- [6]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [7]See Attachment 3.

Table 2 (cont'd) Levels and types of claims and the evidence required to support them - based on evidence of traditional use

Level of claim	Type of claim	Wording of Claim[1]	Evidence required to support claim
GENERAL	▪ Health maintenance, including for example indications/claims relating to nutritional support. ▪ Relief of symptoms (not referring to a named disease, disorder or condition)[2]. ▪ Claims for traditional syndromes and actions[3].	This (tradition) medicine has been traditionally used for (indication) [3].	**Primary evidence**: *One of the following four sources that demonstrates adequate support for the indications claimed·* 1. TGA-approved Pharmacopoeia.[5] 2. TGA-approved Monograph.[5] 3. Three independent written histories of use in the classical or traditional medical literature [4]. 4. Availability through any country's government public dispensaries for the indication claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:

- [1]Or words to this effect.
- [2]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [3] Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations, for example "Shen" not "Kidney" in TCM.
- [4]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support indications/claims.
- [5]See Attachment 3.

Table 3: Levels and types of claims for homoeopathy and the evidence required to support them - based on evidence of traditional use or evidence of traditional practice

Level of claim	Type of claim	Wording of Homoeopathic Claim[1]	Evidence required to support homoeopathic claim
MEDIUM	▪ Health enhancement[2]. ▪ Aids/assists in the management of a symptom complex of a named symptom/disease, disorder or condition.[3] ▪ Relief of symptoms of a named disease, disorder or condition[3].	This homoeopathic medicine has been traditionally used for (indication)[5] , **or**, This homoeopathic medicine has been prepared by traditional methods for (indication) [5,6].	**Primary evidence**: *Two of the following three sources that demonstrate adequate support for the indications claimed:* 1. Well-designed homoeopathic proving of the substance(s) **or** a TGA-approved[7] Homoeopathic Materia Medica and a Homoeopathic Repertory. 2. Three independent written histories of use in the traditional or contemporary homoeopathic literature[4]. **3.** Availability through any country's government public dispensaries for the indications claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence. In addition, records of the set of symptoms provoked by the crude substance may be used. This evidence may only be used in conjunction with the homoeopathic evidence referred to above.

Notes:

- [1]Or words to this effect.
- [2]Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- [3]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [4]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated.
- [5] Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations..
- [6]Where scientific evidence is available for this claim the tradition from which the medicine originated need not be specified.
- [7]See Attachment 3.

Table 3: Levels and types of claims for homoeopathy and the evidence required to support them - based on evidence of traditional use or evidence of traditional practice (cont'd)

Level of claim	Type of claim	Wording of Homoeopathic Claim[1]	Evidence required to support homoeopathic claim
GENERAL	▪ Health maintenance, including for example indications/claims relating to nutritional support. ▪ Relief of symptoms (not referring to a named disease, disorder or condition)[2]. ▪ Claims for traditional syndromes and actions[4].	This homoeopathic medicine has been traditionally used for (indication)[4], **or**, This homoeopathic medicine has been prepared by traditional methods for (indication)[4].	Three independent written histories of use[3] in the traditional or contemporary homoeopathic literature; or homoeopathic provings supporting the indications claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence. In addition, records of the set of symptoms provoked by the crude substance may be used. This evidence may only be used in conjunction with the homoeopathic evidence referred to above.

Notes:

- [1]Or words to this effect.
- [2]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [3]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated.
- [4]Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations..

Table 4: Levels and types of claims for aromatherapy and the evidence required to support them - based on evidence of traditional use

Level of claim	Type of claim	Wording of Claim[1]	Evidence required to support claim
MEDIUM	▪ Health enhancement[2]. ▪ Reduction in frequency of a discrete event. ▪ Aids/assists in the management of a named symptom/disease/ disorder/ condition.[3] ▪ Relief of symptoms of a named disease, disorder or condition[3].	This essential oil has been traditionally used for (indication).[4]	**Primary evidence**: *Two of the following three sources that demonstrate adequate support for the indications claimed:* 1. TGA-approved Pharmacopoeia.[6] TGA-approved Monograph.[6] 2. Three independent written histories of use in the traditional aromatherapy literature.[5] 3. Availability through any country's government public dispensaries for the indication claimed.
GENERAL	▪ Health maintenance ▪ Relief of symptoms (not referring to a named disease, disorder or condition)[3].	This essential oil has been traditionally used for (indication).	Three independent written histories of use in the traditional aromatherapy literature supporting the indications claimed[5].

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:
- [1]Or words to this effect.
- [2]Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- [3]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [4]Where scientific evidence is available for this claim the tradition from which the medicine originated need not be specified.
- [5]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support indications/claims.
- [6]See Attachment 3.

The following information and examples of how to use evidence of traditional use to support indications/claims is an adaptation of the information in the US FTC guidelines, and has been incorporated into these Australian Guidelines.

Indications and claims based on historical or traditional use should be substantiated by confirming scientific evidence, or should be presented in such a way that consumers

understand that the sole basis for the claim is a history of use of the product for a particular purpose. A number of products, particularly herbal products, have a long history of use as traditional medicines to treat certain conditions or symptoms.

Indications and claims based solely on traditional use should be presented carefully to avoid the implication that the product has been scientifically evaluated for efficacy. The degree of qualification necessary to communicate the absence of scientific substantiation for a traditional use claim will depend in large part on consumer understanding of this category of products. As consumer awareness of and experience with "traditional use" supplements evolve, the extent and type of qualification necessary is also likely to change.

There are some situations, however, where traditional use evidence alone will be inadequate to substantiate a claim, even if that claim is carefully qualified to convey the limited nature of the support. In determining the level of substantiation necessary to substantiate a claim, the consequences of a false claim must be taken into consideration. Indications and claims that, if unfounded, could present a substantial risk to consumer health or safety will be held to a higher level of scientific proof.

Sponsors should also make sure that they can support the extent and manner of historical use and be careful not to overstate such use. Sponsors should make sure that the product to be marketed is consistent with the product as traditionally administered. If there are significant differences between the traditional use product and the marketed product, in the form of administration, the formulation of ingredients, the dose, or the indication for which the product has been used, a "traditional use" claim may not be appropriate.

> *Example 1:* The sponsor of a herbal supplement makes the claim, "Ancient folklore remedy used for centuries by Native Americans to aid digestion." The statement about traditional use is accurate and the supplement product is consistent with the formulation of the product as traditionally used. However, if this statement was used in a context which suggested that scientific evidence demonstrates efficacy where no such evidence exists, this would be misleading and, therefore, unacceptable.
>
> *Example 2:* A sponsor wants to market a herbal product that has been used in the same formulation in China as a tonic for improving mental functions. The sponsor prepares the product in a manner consistent with Chinese preparation methods. The claims are, "Traditional Chinese Medicine — Used for Thousands of Years to Bring Mental Clarity and Improve Memory." The product label also contains language that clearly conveys that the efficacy of the product has not been confirmed by research, and that traditional use does not establish that the product will achieve the claimed results. The label is likely to adequately convey the limited nature of support for the claim.

Indications and claims based on scientific evidence

There are various types of indications and claims based on scientific evidence that can be made; they are generally categorised according to the type of information they convey. Additionally, claims can be ranked in relation to the relative strength of the claim and their likely impact on consumers. These rankings provide a basis for the level of scientific evidence which may be required to support each type of claim. In Australia, indications and

claims which may be made about therapeutic goods are categorised into three levels - high, medium and general. Different levels of evidence are required to support each level of claim. Within these three levels there are several different types of indications and claims which may be made. For simplicity, this approach can be summarised as shown in Table 5. A summary of the definitions of the types of claims is provided at Attachment 2 to these guidelines.

There is a wide variety of references, research papers and texts which may be used as sources of evidence to support these indications and claims. Sponsors should make sure that the research on which they rely is relevant to the specific product being promoted and to the specific benefit being claimed. Further guidance for Registrable products is available in the Australian Guidelines for the Registration of Drugs (volume 2) for OTC products, and for complementary medicines, the Australian Guidelines for Complementary Medicines (currently in preparation).

Table 5: Levels and types of claims and the evidence required to support them - based on scientific evidence

Level of claim	Type of claim	Evidence required to support claim
HIGH[1]	▪ Treats/cures/manages any disease/disorder/condition. ▪ Prevention of any disease, disorder or condition. ▪ Treatment of specific named vitamin or mineral deficiency diseases.	High level. Registration only – evaluated by the CMEC, MEC or ADEC.
MEDIUM	▪ Health enhancement[2]. ▪ Reduction of risk of a disease/disorder/condition. ▪ Reduction in frequency of a discrete event. ▪ Aids/assists in the management of a named symptom/disease/disorder/ condition.[3] ▪ Relief of symptoms of a named disease, disorder or condition[3].	Medium level. Sponsor must hold the evidence for Listable goods.
GENERAL	▪ Health maintenance, including nutritional support. ▪ Vitamin or mineral supplementation[4]. ▪ Relief of symptoms (not related to a named disease, disorder or condition)[3].	General level. Sponsor must hold the evidence for Listable goods.

Notes:

- [1]There are some specific exemptions to this table which are not considered to be high level claims. These are listed on the TGA website at www.health.gov.au/tga.
- [2]Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- [3]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [4]Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25 percent of the Recommended Dietary Intake (RDI) for that vitamin or mineral. The RDI in this context refers to the Australian RDI. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. Where vitamins or minerals are the subject of other kinds of

claims, the dose must be consistent with the evidence to support the claim being made. Indications/claims should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level.

REGISTRABLE DISEASES LIST

There is a list of diseases/disorders/conditions about which indications/claims may be made only after evaluation of the product and the claim(s) through Registration of the product. The list refers to serious diseases/disorders/conditions and it applies to indications and claims based on evidence of traditional use, as well as to those based on scientific evidence. The list is known as the 'Registrable disease' list and it applies to medicines but not devices. Decisions made with respect to the Registration of medical devices are based on a different set of categorisations and guidelines.

The definition of a serious disease, disorder or condition is one for which there is a substantial body of medical opinion that the disease (disorder or condition) cannot or should not be diagnosed or treated except under medical advice.

Indications/claims for Registrable diseases may be made under certain circumstances, but only after the safety, quality and efficacy of the product and the claim(s) have been evaluated by the CMEC or other relevant evaluation committee. Where a sponsor seeks to mention a Registrable disease in what would otherwise have been categorised as a medium or general level claim, that claim would become Registrable and the product would require Registration (that is, evaluation by the TGA with the advice of the CMEC, MEC, or ADEC). The 'Registrable disease' list is shown in Table 6.

Table 6: The Registrable disease list (for medicines)

Disease/disorder/condition/action – serious manifestation of	
Abortifacient action.	Infectious diseases, including sexually transmitted diseases.
Cardiovascular diseases.	Insomnia, persistent.
Dental and periodontal disease.	Mental diseases, ailments or defects, including substance abuse.
Diseases of joint, bone, collagen, and rheumatic disease.	Metabolic disorders.
Diseases of the eye or ear likely to lead to severe impairment, blindness or deafness.	Musculoskeletal diseases.
Diseases of the liver, biliary system or pancreas.	Neoplastic disease (all cancers).
Endocrine diseases and conditions, including diabetes and prostatic disease.	Nervous system diseases.
Gastrointestinal diseases.	Renal diseases, diseases of the genito-urinary tract.
Haematological disorders and diseases.	Respiratory diseases.
Immune disorders and diseases.	Skin diseases.
Other	
Immunisation	Poisoning, venomous bites and stings – treatment of.

There are some exceptions to the Registrable disease list, whereby diseases, disorders or conditions which would normally require Registration may be mentioned in indications and claims on Listed medicines. These exceptions will be listed in the new version of the Electronic Lodgement Facility (ELF3) coded indications and are provided in hard copy

format on the TGA website at www.health.gov.au/tga. Where there is no suitable coded indication in ELFversion 2, these new indications and claims may be entered as free text in item 27.

IN CONCLUSION

Further advice on the whole or any part of these Guidelines can be sought from the TGA, the major industry associations, and from regulatory affairs consultants.

ATTACHMENT 1

GLOSSARY OF TERMS USED IN THESE GUIDELINES

Blinding
Blinding (also called masking) is a procedure in which one or more parties in a clinical trial are kept unaware of the treatment assignment(s). Blinding is used so that neither the patients' nor staff's expectations about the medicine or treatment under investigation can influence the outcome.

Case study
In depth description of the factors related to a disease, disorder or condition in a specific individual (CHC).

Case-control study
A study that starts with identification of people with the disease, disorder or condition of interest (the cases) and a suitable control group without the disease or outcome (the controls). The relationship of an attribute (medicine, treatment, exposure or risk factor) to the outcome of interest is examined by comparing the frequency or level of the attribute in the cases and in the controls. For example, to determine whether thalidomide caused birth defects, a group of children with birth defects (cases) could be compared to a group of children without birth defects (controls). The groups would then be compared with respect to the proportion exposed to thalidomide through their mothers taking the tablets. Case-control studies are sometimes described as being retrospective as they are always performed looking back in time.

Clinical significance
The quality of a study's outcome that convinces physicians to modify or maintain their current practice of medicine. The assessment of clinical significance is usually based on the size of the effect observed, the quality of the study that yielded the data, and the probability that the effect is a true one. Clinical significance is not the same as statistical significance; a finding in a study may demonstrate a statistical difference in an attribute under review but this may have no impact clinically.

Clinical trial/clinical study (synonym: intervention study)
A planned study in humans designed to discover or verify:

- the clinical, pharmacological and/or other pharmacodynamic effects of a medicine or treatment; and/or
- to identify any adverse reactions to a medicine or treatment; and/or
- to study absorption, distribution, metabolism and excretion of a medicine or treatment,

with the object of ascertaining its safety and/or efficacy.

Clinical trials of experimental medicines proceed through four phases:

- In Phase I, researchers test a new medicine or treatment in a small group of normal, healthy volunteers (20-80) for the first time to evaluate its safety, determine a safe dosage range and identify side effects.
- In Phase II, the study drug or treatment is given to a larger group of people with the disease/disorder of interest (100-300) to see if it is effective and to further evaluate its safety.

- In Phase III studies, the study drug or treatment is given to large groups of people with the disease/disorder of interest (1,000 – 3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatment and collect information that will allow the drug or treatment to be used safely.
- Phase IV studies are done after the medicine or treatment has been marketed following regulatory approval. These studies continue testing the study drug or treatment to collect information about their effect in various populations and any side effects associated with long-term use.

Cochrane Review
A Cochrane Review is a systematic, up-to-date summary of reliable evidence of the benefits and risks of healthcare. For a review to be called a "Cochrane Review" it must be in the Parent database maintained by the Cochrane Collaboration. The Cochrane Collaboration is an international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of healthcare interventions.

Cohort study (synonyms: follow-up, incidence, longitudinal, prospective study)
An observational study in which a defined group of people (the cohort) is followed over time. The outcomes of people in subsets of this cohort are compared, (e.g. to examine people who were exposed or not exposed, or exposed at different levels, to a particular intervention or other factor of interest). A cohort can be assembled in the present and followed into the future (this would be a prospective study or a "concurrent cohort study"), or the cohort could be identified from past records and followed from the time of those records to the present (this would be a retrospective study or a "historical cohort study"). Because random allocation is not used, matching or statistical adjustment at the analysis stage must be used to minimise the influence of factors other than the intervention or factor of interest.

Condition: A simplified description for a disorder, which is a derangement or abnormality of function.

Control
In clinical trials comparing two or more interventions, a control is a person in the comparison group that does not receive the medicine or treatment under evaluation. Instead that person receives a *placebo*, no intervention, usual care or another form of care. In case-control studies, a control is a person in the comparison group without the disease or outcome of interest.

In statistics, to control means to adjust for or take into account extraneous influences or observations.

Controlled clinical trial
Refers to a study that compares one or more intervention groups to one or more comparison (control) groups. Whilst not all controlled studies are randomised, all randomised trials are controlled.

Crossover trial
This is a research design in which subjects receive a number of treatments in sequence. Generally, this means that all subjects have an equal chance during the trial of experiencing both treatment and placebo dosages without direct knowledge, instead of either placebo or the treatment. Subjects may be transferred directly from one treatment to another or may have a

washout period in between test treatments. This type of trial can be randomised so that all subjects don't get the alternative treatments in the same order.

Disease: Any deviation or interruption of the normal structure or function of any part, organ or system (or combination thereof) of the body that is manifested by a characteristic set of symptoms and signs and whose aetiology, pathology and prognosis may be known or unknown.

Disorder: a derangement or abnormality of function.

Dosage form
The pharmaceutical form in which a product is presented for therapeutic administration (e.g. tablet, cream).

Dosage regimen
The number of doses per given time period, the time that elapses between doses or the quantity of a medicine that is given at each specific time of dosing.

Double blind
Neither the participants in a trial nor the investigators (outcome assessors) are aware of which intervention the participants are given during the course of the trial.

Efficacy
A relative concept referring to the ability of a medicine or treatment to achieve a beneficial clinical effect. This may be measured or evaluated using objective or subjective parameters.

Endpoint
An indicator measured in a patient or biological sample to assess safety, efficacy or another trial objective. Also defined as the final trial objective by some authors.

Epidemiology
The study of the distribution and determinants of health-related states or events in specified populations.

Evidence-based textbook
A textbook based on a critical and systematic review of published data, not simply on the opinions of the author(s).

Good clinical practice
A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

Placebo
An inactive substance or treatment that supposedly has no treatment value. It is given to participants in clinical trials as a control against which to compare the effects of the test substance. In practice, placebos may also have positive or negative effects on trial participants.

Population studies
Investigations of a disease or condition using subjects from a defined population. A population is a closely distributed grouping from a single community that is characterised by both genetic and cultural continuity through several generations.

Protocol
All clinical trials are based on a protocol, which describes who may participate in a trial, the length of a trial and the schedule of tests, procedures, medications and dosages.

Randomisation
The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomised controlled trial (RCT)
An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups.

Sign: any objective evidence of a disease, that is, such evidence as is perceptible to the examining physician, as opposed to the subjective sensations (symptoms) of the patient.

Single blind
A clinical trial where the participants are unaware of the whether they are receiving the placebo or active medicine or treatment.

Site
This refers to the place where a clinical trial is conducted. When a clinical trial is conducted at more than one site, but using the same protocol, it is referred to as a multi-site or multi-centre trial.

Statistical significance
The probability that an event or difference is real or occurred by chance alone. It does not indicate whether the difference is small or large, important or trivial. The level of statistical significance depends on the number of patients studied or observations made, as well as the magnitude of difference observed. Statistical significance observed in a clinical trial does not necessarily imply clinical significance.

Subject/trial subject
An individual who participates in a clinical trial, either as a recipient of the medicine or treatment, or as a control.

Syndrome: A set of symptoms which occur together; a symptom complex.

Symptom: any subjective evidence of disease or of a patient's condition, that is, such evidence as perceived by the patient.

Systematic review
An analysis of a large number of clinical trials (sometimes known as a 'meta-analysis') aimed at looking for an overall pattern in the trial results. Cochrane Reviews are examples of such systematic reviews. In a systematic analysis only those trials which meet a number of pre-set

conditions in relation to research design (e.g. sample size, randomisation) are included in the final meta-analysis.

Therapeutic good

The *Therapeutic Goods Act 1989* defines a therapeutic good as follows:

"therapeutic goods means goods:

(a) that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be:
  (i) for therapeutic use; or
  (ii) for use as an ingredient or component in the manufacture of therapeutic goods; or
  (iii) for use as a container or part of a container for goods of the kind referred to in subparagraph (i) or (ii); or

(b) included in a class of goods the sole or principal use of which is, or ordinarily is, a therapeutic use or a use of a kind referred to in subparagraph (a)(ii) or (iii);

and includes goods declared to be therapeutic goods under an order in force under section 7, but does not include:

(c) goods declared not to be therapeutic goods under an order in force under section 7; or

(d) goods in respect of which such an order is in force, being an order that declares the goods not to be therapeutic goods when used, advertised, or presented for supply in the way specified in the order where the goods are used, advertised, or presented for supply in that way; or

(e) goods for which there is a prescribed standard in the Australia New Zealand Food Standards Code as defined in subsection 3(1) of the *Australia New Zealand Food Authority Act 1991*; or

(f) goods which, in Australia or New Zealand, have a tradition of use as foods for humans in the form in which they are presented."

Therapeutic use

The *Therapeutic Goods Act 1989* defines therapeutic use as follows:

"therapeutic use means use in or in connection with:

(a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons or animals; or

(b) influencing, inhibiting or modifying a physiological process in persons or animals; or

(c) testing the susceptibility of persons or animals to a disease or ailment; or

(d) influencing, controlling or preventing conception in persons; or

(e) testing for pregnancy in persons; or

(f) the replacement or modification of parts of the anatomy in persons or animals."

Washout period

The stage in a cross-over trial where treatment is withdrawn before a second treatment is given. This is usually necessary to counteract the possibility that the first substance can continue to affect the subject for some time after it is withdrawn.

Acknowledgements:

This glossary has been adapted from that prepared by the Australasian Cochrane Centre, based at the Monash and Flinders Medical Centres.

Additional information was obtained from:

- Australian Guidelines for the Registration of Drugs. Volume 1. Prescription Medicines. Canberra: Therapeutic Goods Administration
- Complementary Healthcare Council of Australia
- Miller-Keane Encyclopaedia and Dictionary of Medicine, Nursing & Allied Health. 6th Edition. Philadelphia: Saunders. 1997
- Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95). TGA, DSEB (2000)
- Spilker B. 1996. Guide to clinical trials. Philadelphia: Lippincott-Raven Publishers
- US National Institute of Health, Clinical Trials service (www.clinicaltrials.gov/)

ATTACHMENT 2

DEFINITIONS – TYPES OF CLAIMS

Aids/Assists claims – a claim which describes how a product or substance may aid/assist in the management of a named symptom/disease or disorder.

Discrete events claims – a claim which refers to the ability of a product or substance to reduce the frequency of a discrete event such as migraine.

Disease management claim – a claim that a product or substance can treat, cure or manage a particular disease, disorder, condition or ailment.

Preventive claim –a claim which relates to preventing a particular disease, disorder, condition, symptom or ailment.

Risk reduction claim - a claim which relates to reducing the risk of a particular disease, disorder, condition, symptom or ailment.

Health enhancement claim - health maintenance claims which relate to health enhancement for normal healthy people, such as improving, promoting, enhancing or optimising (or words to that effect) body organs or systems.

Health maintenance claim –a claim which refers to an effect a product or substance may have in maintaining health (or words to that effect), but not including health enhancement or prevention claims. Health maintenance claims may also relate to the normal physiological consequences for good health associated with a product or substance, or to the provision of nutritional support and to the use of the terms, cleansing, detoxification and tonic.

Symptom claim – a claim which relates specifically to the temporary relief of a particular symptom. All symptom claims must be accompanied by the statement "If symptoms persist consult your healthcare practitioner" or words to that effect.

Claims relating to specific named vitamin or mineral deficiency diseases – claims which refer to the name of a vitamin or mineral and a recognised deficiency disease.

Claims relating to vitamin or mineral supplementation – claims that refer to supplemental intakes of the vitamin or mineral. Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25 percent of the Recommended Dietary Intake (RDI) for that vitamin or mineral. The RDI in this context refers to the Australian RDI. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. Vitamin and mineral claims of any kind should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level.

ATTACHMENT 3

TGA–APPROVED TEXTS

MONOGRAPHS

- Blumenthal M et al (eds) (2000) Herbal Medicine - Expanded *Commission E monographs,* American Botanical Council, Austin, Texas. **(Note: Commission E monographs may constitute medium level evidence. However, only positive monographs can be used as positive evidence to support claims.)**
- European Scientific Co-operative on Phytotherapy (ESCOP) series (1996) *Monographs on the Medicinal Uses of Plant Drugs*, ESCOP, Exeter.
- World Health Organization (WHO) (1999) *Monographs on Selected Medicinal Plants,* Volume 1, WHO, Geneva.
- Yu HC, Kosuna K and Haga M (Eds) (1997) *Perilla: the Genus Perilla*, Harwood Academic Publishers, Amsterdam.

PHARMACOPOEAS

- *British Herbal Pharmacopoeia* (1996) 4th edition, British Herbal Medicines Association, West Yorks, England.
- *European Pharmacopoeia* (1997) 3rd edition, Council of Europe, Strasbourg.
- *Martindale: the Extra Pharmacopoeia* 91996) 31st edition, Pharmaceutical Press, London.
- *The British Pharmaceutical Codex*, Pharmaceutical Press, London.
- *The British Pharmacopoeia* (1998), Her Majesty's Stationery Office, London.
- *The United States Pharmacopeia and National Formulary* USP24/NF19 (2000) USP Convention Inc, Rockville, Maryland.
- *Pharmacopoeia of the People's Republic of China* (1997), Vol 1.

Other TGA-approved pharmacopoeias on advice from expert committees.
NOTE add in UK homoeopathic pharmacopoeia.

MATERIA MEDICA AND REPERTORY

- Boericke W (1927) *Pocket Manual of Homoeopathic Materia Medica, comprising the characteristic and guiding symptoms of all remedies (clinical and pathogenetic)*, Boericke and Runyon Inc, New York, USA.
- Boger CM (1983) *Boenninghausen's Characteristics and Repertory*, B Jain, New Dehli.
- Boger CM (1992) *Boenninghausen's Characteristics Materia Medica and Repertory with Word Index*, Jain Publishing, New Dehli.
- Julian OA (1979) *Materia Medica of New Homoeopathic Remedies*, Beaconsfield Publishers, Beaconsfield, Bucks, UK.
- Kent JT (1935) *Repertory of the Homoeopathic Materia Medica*, Enrart & Karl, Chicago.
- Kent JT (1978) *Repertory of the Homoeopathic Materia Medica*, 6th American edition, Jain Publishing, New Dehli.
- Murphy R (1999) *Lotus Materia Medica*, 2nd edition, Lotus Star Academy, Colorado, United States of America.
- Reckeweg HH (1991) *Materia Medica*, volume 1, Aurelia Verlag, Baden Baden, Germany, ISBN 3-922907-16-4.

- Vermeulen F (1997) *Concordant Materia Medica*, 2nd edition, Emryss bv, Haarlem, The Netherlands.
- Vermeulen F ( ) *Synoptic Materia Medica,* volumes 1 and 2, further details needed.